Persistence of MB Isoenzyme of Creatine Phosphokinase in the Serum after Minor Iatrogenic Cardiac Trauma

Absence of Postmortem Evidence of Myocardial Infarction


SUMMARY

The specificity of serum CPK-MB for acute myocardial infarction was examined by retrospective analysis of 401 consecutive patients admitted to a Coronary Care Unit over a three and one-half year period with suspected infarction in whom the isoenzyme was subsequently detected. Four patients (1%) who died during the hospital admission had no autopsy evidence of acute myocardial infarction. All four had experienced mild iatrogenic cardiac trauma, following which serum CPK-MB persisted for at least 24 hours. In one patient, a permanent pacemaker had been inserted by the transmediastinal approach. Two patients had been subjected to closed chest cardiac massage and intracardiac puncture, and one to external cardiac massage alone. The findings suggest that persistent identification of serum CPK-MB, although specific for myocardial necrosis, cannot be regarded as diagnostic of myocardial infarction. The implications of this are important to treatment of patients after cardiopulmonary resuscitation and operative trauma to the heart.

Additional Indexing Words:
Cardiac surgery
Cardiopulmonary resuscitation
Cardiac pacemaker

The diagnosis of acute myocardial infarction (AMI) from clinical1,2 electrocardiographic,3 and total serum enzyme4-8 data is often difficult. The ability to identify isoenzymes of creatine phosphokinase (CPK)9 and lactic dehydrogenase (LDH)7 in the serum has facilitated its recognition in both non-9,10 surgical and surgical patients.10

In the absence of clinically recognizable skeletal muscle disorders, detection in the serum of the myocardial-specific (MB) isoenzyme of CPK has been thought to be specific for myocardial damage.8,9 Moreover, its persistent identification, especially in the perioperative period, has been thought to indicate AMI.10

A subgroup of patients was recognized in whom detection of serum CPK-MB was not associated with AMI but with myocardial necrosis secondary to cardiac trauma. The implication of these findings for the diagnosis of AMI after cardiopulmonary resuscitation and cardiac surgery constitutes the reason for this report.

Methods

Patients

Those patients admitted to the Coronary Care Unit of Duke University Medical Center between January 1, 1971, and June 30, 1974, with suspected AMI constitute the study population. The patients were managed routinely: Twelve-lead electrocardiograms were taken daily and venous blood samples for analysis of serum enzymes and isoenzymes drawn twice daily (at 6:00 A.M. and 6:00 P.M.).

Biochemical Procedures

Blood samples were withdrawn by the vacutainer technique, into a tube containing EDTA as anticoagulant. Plasma was immediately separated from the cells by centrifugation, and the plasma samples frozen until enzyme and isoenzyme determinations were made within 24 hours.

Plasma CPK was determined by the method of Rosalki,11 using the modified reagent substrate prepared by Eskalab (normal value for the laboratory 0-130 I.U.). Determinations were carried out on the Eskalab Clinical Chemistry System (Smith-Kline Instruments Inc., Palo Alto, California).

Isoenzymes of CPK and LDH were determined electrophoretically on a supporting medium of 1% ionagar, using methods described by Nerenberg and Pogojeff12 for LDH,

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and Roe et al. for CPK. The LDH isoenzymes were visualized by precipitation of formazan, while CPK isoenzymes were quantitated fluorimetrically, using the Clifford 445 Densicom (Clifford Instruments Inc., Natick, Mass.). Myocardial infarction is characterized by appearance of serum CPK-MB (normal 0 I. U.) and elevation of LDH isoenzyme 1 to a level greater than LDH isoenzyme 2.

Pathological Methods

For gross examination, formalin-fixed hearts were sectioned by four equally spaced cross cuts through the ventricles and the interventricular septum between the apex and base. At each level, blocks were taken from the anterior, lateral and posterior regions of the left ventricle, anteriorly and posteriorly in the interventricular septum, and in the region of the right ventricle. For microscopic examination, these blocks were fixed in Zenker’s solution, embedded, and stained with hematoxylin and eosin and with Masson’s stain.

Results

Over the 3½ year period, serum CPK-MB was identified in 401 patients admitted to the Coronary Care Unit with a diagnosis of suspected AMI. Of these, 274 patients (68%) had electrocardiographic evidence of AMI, developing new Q waves, or in the absence of prior tracings, evolutionary ST-segment and T-wave changes indicative of epicardial injury associated with prior QRS indication of infarction.

Of the 127 patients (32%) who had serum CPK-MB but did not show electrocardiographic changes diagnostic of AMI, 18 died. Autopsy was performed in 11 of these 18, and postmortem evidence of AMI found in six.

Five patients had no autopsy evidence of AMI. One died approximately eight hours after the onset of acute dyspnea and chest pain. He remained hypotensive and in frank pulmonary edema until his death. Although at autopsy only old myocardial infarction was found, it is most likely that AMI was not identified because death preceded the development of morphological changes. Serum CPK-MB, therefore, could not be considered to be falsely-positive in this patient.

A history of iatrogenic cardiac trauma was present in the other four patients without AMI at autopsy. The relevant clinical data and autopsy findings on these four patients is presented in table 1. Their enzyme and isoenzyme levels over the three days after trauma are shown in table 2. After occurrence of cardiac trauma, all four had serum CPK-MB identified for at least 24 hours, and they survived a sufficient period for AMI to be recognized at autopsy. In none of the four did there appear to have been extensive myocardial damage. No greater than the usual inflammatory reaction was identified about the pacemaker electrodes in patient 1, and the needle tracks in patients 2 and 3 had not traumatized major coronary vessels. Needle tracks were thought to be responsible for two small areas of midseptal (1.2 cm diameter) and posterior left ventricular (0.5 cm diameter) necrosis in patient 2 which did not follow any vascular pattern. Autopsy examination in patient 4 showed a similar minute area of necrosis in the posterior left ventricular wall. This was again thought to be secondary to resuscitation or hypotension rather than indicative of AMI. The cause of death in three of these four patients (patients 1, 3, 4) was thought to be bronchopneumonia. No cause of death was identified in patient 2.

Discussion

The three isoenzymes of CPK differ in their dimer structure. The BB and MM isoenzymes are located primarily in brain and skeletal muscle, respectively, although significant concentrations of the MM form are present in the heart. The hybrid MB isoenzyme is detected almost exclusively in the myocardium, and the small proportion of CPK-MB in skeletal muscle has been reported to vary between 0–20% of its concentration in the heart.

Normally, CPK-MB cannot be detected in the serum. It may be released from skeletal muscle in such disorders as progressive muscular dystrophy, dermatomyositis, or conditions associated with myoglobinuria, but these conditions can be clinically recognized. Its importance for the diagnosis of AMI rests chiefly upon its specificity for myocardial damage. Wagner et al. found only a 1% incidence of false positivity for serum CPK-MB in the diagnosis of AMI in a Coronary Care Unit. They showed that the isoenzyme is present in the serum for periods of between 24–72 hours after an initial appearance at 2–12 hours after the onset of symptoms of AMI.

The myocardial-specificity of CPK-MB is even more valuable after cardiac surgery when other criteria for AMI have many limitations. In this period, cardiac pain may be either indistinguishable from that of the operative wound or masked by analgesics and the true significance of fever, tachycardia or hypotension also not appreciated, 2) most patients develop ST-segment and T-wave changes, often due to other causes such as pericarditis or myocardial ischemia without infarction, and 3) total serum CPK rises for approximately 72 hours because of the skeletal muscle trauma with operation. Identification of serum CPK-MB for the accurate diagnosis of AMI complicating myocardial revascularization in potentially susceptible patients is especially important. In a previous study of 100 consecutive patients undergoing coronary artery bypass grafting at this institution, 22 of 30 patients (74%) who showed serum CPK-MB without electrocardiographic changes of AMI did not have isoenzyme detectable after 18 hours.
Table 1

Relevant Clinical and Autopsy Details of the Four Patients in Whom Serum CPK-MB Persisted After Cardiac Trauma Without Electrocardiographic or Autopsy Evidence of AMI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Indication for CCU admission</th>
<th>Cardiac trauma</th>
<th>Survival after trauma</th>
<th>Myocardium</th>
<th>Autopsy findings</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>94</td>
<td>Syncope: complete heart block</td>
<td>Permanent pacemaker implantation (transmediastinal approach)</td>
<td>7 days</td>
<td>Corkscrew pacemaker leads in LV apex Fibroed conduction system No acute myocardial necrosis</td>
<td>Bronchopneumonia Adenocarcinoma colon Diffuse marked coronary atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>69</td>
<td>Cardiac arrest in ER</td>
<td>E.C.M. I.C.P.</td>
<td>60 hours</td>
<td>Two hemorrhagic and necrotic areas in mid-septum (1.2 cm diam) and posterior LV (0.5 cm diam)</td>
<td>Diffuse marked coronary atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>73</td>
<td>Respiratory distress: then cardiac arrest in ER</td>
<td>E.C.M. I.C.P.</td>
<td>4 days</td>
<td>Needle tracks</td>
<td>Centrilobular emphysema Necrotizing bronchopneumonia Cerebral contusion 30% occlusion proximal right coronary artery</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>74</td>
<td>Dyspnea and hypotension (cardiac arrest in CCU)</td>
<td>E.C.M.</td>
<td>40 hours</td>
<td>Old anteroseptal and anterolateral infarction Minute necrotic area (0.3 mm diam) in posterior LV</td>
<td>Centrilobular emphysema Bronchopneumonia Diffuse moderate coronary atherosclerosis</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCU = coronary care unit; ER = emergency room; E.C.M. = external cardiac massage; I.C.P. = intracardiac puncture; LV = left ventricle.
Table 2
Levels of Total Serum CPK (I.U.), its MB Isoenzyme (I.U.), and Relative Levels of LDH Isoenzymes 1 and 2 Following Cardiac Trauma to Four Patients Without Autopsy Evidence of AMI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Trauma</th>
<th>Enzyme</th>
<th>6:00 AM</th>
<th>6:00 PM</th>
<th>6:00 PM</th>
<th>6:00 PM</th>
<th>6:00 AM</th>
<th>6:00 PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insertion perm. pacemaker</td>
<td>Total CPK</td>
<td>1081</td>
<td>1195</td>
<td>846</td>
<td>211</td>
<td>260</td>
<td>333</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPK-MB</td>
<td>295</td>
<td>161</td>
<td>111</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDH isoenzymes</td>
<td>1 &lt; 2</td>
<td>1 &lt; 2</td>
<td>1 &lt; 2</td>
<td>1 = 2</td>
<td>1 &lt; 2</td>
<td>1 &lt; 2</td>
</tr>
<tr>
<td>2</td>
<td>E.C.M.</td>
<td>Total CPK</td>
<td>748</td>
<td>5613</td>
<td>3629</td>
<td>3223</td>
<td>4888</td>
<td>5613</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPK-MB</td>
<td>127</td>
<td>786</td>
<td>367</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDH isoenzymes</td>
<td>1 = 2</td>
<td>1 = 2</td>
<td>1 &gt; 2</td>
<td>1 &gt; 2</td>
<td>1 &lt; 2</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td>3</td>
<td>E.C.M.</td>
<td>Total CPK</td>
<td>1760</td>
<td>2363</td>
<td>2771</td>
<td>2374</td>
<td>1951</td>
<td>1707</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPK-MB</td>
<td>28</td>
<td>76</td>
<td>47</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDH isoenzymes</td>
<td>1 &gt; 2</td>
<td>1 &gt; 2</td>
<td>1 &gt; 2</td>
<td>1 &gt; 2</td>
<td>1 = 2</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td>4</td>
<td>E.C.M.</td>
<td>Total CPK</td>
<td>1073</td>
<td>1397</td>
<td>3145</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPK-MB</td>
<td>96</td>
<td>29</td>
<td>220</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDH isoenzymes</td>
<td>1 = 2</td>
<td>1 &lt; 2</td>
<td>1 = 2</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: E.C.M. = external cardiac massage; I.C.P. = intracardiac puncture.

and usually after a much shorter postoperative period. Previous studies in chronically prepared awake dogs subjected to left circumflex coronary artery occlusion showed that serum CPK-MB appeared immediately after release of a 45 minute occlusion. However, appearance of the isoenzyme was delayed four to nine hours (and the extent of myocardial necrosis much greater) after a permanent occlusion. This suggests that peripheral detection of serum CPK-MB depends partly upon the adequacy of myocardial perfusion. The clinical situation after myocardial revascularization is probably analogous. After revascularization procedures, the early transient appearance of the isoenzyme has been thought to indicate minimal or mild myocardial injury. Persistence of CPK-MB has been thought to probably indicate AMI.

This present study showed that six of the eleven autopsy patients with serum CPK-MB but no electrocardiographic evidence of AMI had, in fact, sustained infarction. This confirms the previous findings suggesting the relative insensitivity of the electrocardiogram as compared with serum CPK-MB in the diagnosis of AMI. However, this updated analysis has provided more information concerning the specificity of serum CPK-MB. The incidence of false-positivity for AMI has again been shown to be 1%. However, the true incidence may well be higher as pathological data was available on only 11 of the 127 patients with serum CPK-MB and nondiagnostic electrocardiograms. Of great importance is the recognition that myocardial trauma may cause persistent presence of serum CPK-MB. Proof is lacking, but the isoenzyme was presumably released from the myocardium in all four cases, although trauma to the heart was not extensive. Skeletal muscle release was unlikely as serum CPK-MB is not detectable after repeated cardioversions when the total CPK is grossly elevated.

It is therefore necessary to re-evaluate the significance of serum CPK-MB after cardiac trauma. The test remains diagnostically useful for the identification of myocardial damage. However, persistent identification of serum CPK-MB after pacemaker implantation or cardiopulmonary resuscitation should not be considered to reliably indicate AMI, as it may reflect myocardial release consequent upon the trauma itself. It may also be that after other cardiac surgical procedures such as venting or ventriculotomy (which might accompany revascularization), persistence of serum CPK-MB may not always indicate perioperative infarction. This last statement is speculative and requires further investigation by the correlation of isoenzymatic and pathological findings in a series of patients.

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